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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MONTANARI, DAVID A	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/237,291	YOUNG ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-20,23-26,31-34,37-43,46,47 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-20,23-26,31-34,37-43,46,47 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants arguments and amendments filed on 11/3/2008 have been entered.

2. Claims 18, 23, 37, 40 and 52 are amended.

3. The previous 35 USC 103(a) rejection is withdrawn in view of Applicants' arguments and a new 35 USC 103(a) rejection is made below.

4. Claim 18-20, 23-26, 31-34, 37-43, 46, 47 and 52 are examined in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 18-20, 23-26, 31-34, 37-43, 46, 47, and 52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Dao et al. (01/15/1997, Blood, Vol. 89, pgs. 446-456), Young et al. (09/01/1996, Blood, Vol. 88, pgs. 1619-1631) and Zauli et al. (1997, Blood,Vol. 89(3), pgs. 883-895).

Claims 18-20, 23-27, 31-34, 37-43, 46-47, and 52 are drawn to a method for obtaining genetically modified human pluripotent hematopoietic stem cells, comprising contacting a vector comprising a polynucleotide sequence encoding a heterologous gene with a population of human pluripotent hematopoietic stem cells cultured with fibronectin and in the presence of an effective amount of a mpl ligand and a flt3 ligand, each ligand provided in a concentration range of about

0.1 ng/mL to about 500 ng/mL, wherein said vector is selected from the group consisting of retroviral vectors, adenoviral vectors, and adeno-associated viral vectors and wherein said human pluripotent hematopoietic stem cells are $CD34^{+}$ $Thy\text{-}1^{+}$ Lin^{-} cells and can differentiate into any hematopoietic cell type; and obtaining said modified human pluripotent hematopoietic stem cells.

With respect to claims 18, 23, 32, 37 and 52 Dao et al. teach human CD34+ progenitor cells transduced with retrovirus and cultured with FTL3 ligand (FL), to test whether FL might be able to replace the maintenance role provided by stromal support (pg. 446, Abstract). Dao continues to teach that said cells where cultured in the presence of interleukin-3 (IL-3) with respect to claims 20, 25, 40 and 41, IL-6, and stem cell factor (SCF), and that the retrovirus contained the bacterial neomyocin resistance gene (pg. 446 Abstract, and pg. 447, col. 2 parag. 4 lines 1-9). With respect to claims 33 and 46 the specification defines a marker gene as a neomyocin resistance gene on pg. 14 lines 21-22. Dao teaches that concentrations used for the substrates in their experiment were 100 ng/ml for FLT3 (pg. 447 col. 1 parag. 3), 10 ng/ml for IL3 (pg. 449 col 1, Fig. 1 text) and 50 ng/ml for SCF (pg. 449 col 1, Fig. 1 text). Collectively these concentrations fall within all of the claimed concentration ranges for each substrate, and particularly for claims 31, 38 and 42. Dao obtained transduced CD34+ cells and were examined with colony-forming assay (pg. 448, Fig. 1 and Table 1). Dao continues that "the combination of fibronectin, to enhance gene transfer, and FL, to support progenitor survival, may ultimately replace the use of patient-derived stromal layers" (pg. 455, col. 1 parag. 2). Dao et al. do not teach using cells cultured with an mpl ligand and fibronectin.

However at the time of filing it was known to one of ordinary skill in the art that fibronectin in combination with an mpl ligand such as TPO enhances adhesion in CD34+ cells. Zauli et al. teach that CD34+ cells, when cultured on fibronectin coated plates and in the presence of TPO significantly enhanced cellular adhesion to the coated plate (pg. 893 col. 1 parag. 2). Zauli continues to teach that adhesion interaction may play a primary role in the process of megakaryocyte development and maturation (pg. 890 col. 2 parag. 2, last sentence). Zauli et al. do not teach the culture of $CD34^+$ Thy-1^+ Lin^- cells in the presence of an mpl ligand.

However, at the time of filing it was known to one of ordinary skill in the art that mpl ligands were known to enhance the transduction of $CD34^+$ Thy-1^+ Lin^- cells. With respect to claims 18, 23, 37 and 52 Young et al. teach pluripotent $CD34^+$ Thy-1 Lin^- cells cultured with stromal support and thrombopoietin (TPO, an mpl ligand), for claims 19 and 26 c-kit ligand and for claims 24 and 39, LIF (pg. 1620 col. 2 parag. 1 and parag. 5). Young et al. continue to teach that TPO stimulated division of $CD34^+$ Thy-1 Lin^- cells, and further enhanced division when combined with IL-3 or c-kit ligand (pg. 1621 Fig. 1). With regard to claim 34 Young continues that when TPO was combined with IL-3, cell production was enhanced 3-fold compared to TPO alone (pg. 1625, col. 1 lines 4-9). Young teaches that concentrations used for the substrates in their experiment were 10 ng/ml for IL-3 (pg. 1620 col. 2 parag. 1), 10 ng/ml for LIF (pg. 1620 col. 2 parag. 1), 10 ng/ml and 100 ng/ml for TPO (pg. 1620 col. 2 parag. 5) and 10 ng/ml for IL-6 (pg. 1620 col. 2 parag. 5). Collectively these concentrations fall within all of the claimed concentration ranges for each substrate, and particularly for claims 31, 38 and 42. Young continues that "to transduce hematopoietic stem cells with exogenous genes using retroviral vectors, there is a requirement to induce cycling of quiescent cells without inducing

differentiation. The effect we demonstrated here, that TPO activates PHP into cycle, has important implications for gene transduction into hematopoietic stem cells" (pg. 1630 col. 1 last parag. bridge col. 2 lines 1-2). With respect to claim 47 Young continues to teach that TPO will be useful for increasing entry of therapeutic genes into PHP (pg. 1619 col. 2 parag. 2 last sentence).

Thus, at the time of filing the ordinary artisan would have found it *prima facie* obvious to combine the teachings of Dao regarding the use of fibronectin in combination with FL to eliminate the need for stromal support with the teachings of Zauli et al. regarding the usefulness of fibronectin in the presence of TPO to enhance megakarycotye maturation and development with the teachings of Young et al. regarding the improved retroviral transduction of $CD34^+$ Thy-l^+ Lin^- cells that are cultured with both a FLT3 ligand and a mpl ligand such as TPO. Further motivation is provide by Young teaching that $CD34^+$ Thy-l^+ Lin^- cells cultured with TPO have enhanced cell production, that a receptor for TPO has been found on $CD34^+$ Thy-l^+ Lin^- cells and that TPO can aid in retrovirus-mediated transduction of hematopoietic stem cells. Thus the combined teachings of Dao and Young would both motivate and teach the ordinary artisan to make and use the claimed invention.

Thus the cited art provides a clear *prima facie* case of obviousness.

Response to Arguments

Applicants Arguments

Applicants argue in amendment filed on 11/3/2008 that the Examiner alleges that Dao suggests the use of fibronectin to enhance gene transfer, and that the combination of fibronectin and flt3 ligand (FL) may ultimately replace the use of patient-derived stromal layers (*Office Action dated November 3, 2005,* at p. 3). Applicants continue that the Examiner's interpretation of Dao would lead an ordinarily skilled artisan to expect higher transduction efficiency of hematopoietic stem cells (HSCs) infected in the presence of fibronectin and fit3 ligand (FL) compared to HSCs infected in the presence of FL alone. Applicants argue though, that as demonstrated by the present application, the exact opposite effect is achieved (*Specification,* at Example 9, Figure 9). Applicants argue that transduction of HSCs in the presence of only IL3, IL6, leukemia inhibitory factor (LIF), and FL resulted in 1.8% of transduced cells, and the addition of Retronectin ™ did not increase the efficiency (*Id.,* at Figure 9). Accordingly, Applicants respectfully assert that the specification demonstrated the absence of an expected property, e.g., the absence of enhanced gene transfer into HSCs in the presence of fibronectin. These arguments are not persuasive.

Response

While Applicants may have discovered unexpected properties the claimed methods do not relate to the enhancement of gene transfer as Applicants argue, and further there is nothing unexpected or unpredictable about the claimed limitations involving the transduction of cells with a viral vector. There are four independent claims in the instant Application with claims 18, 23 and 52 drawn to methods for genetically modifying human pluripotent hematopoietic stem cells and claim 37 reciting a method of transducing human pluripotent CD34 Thy-1 lin hematopoietic stem cells. Further a reading of each of these claims simply recites the culture

conditions with which to contact the cells with an expression vector. In combination, Dao and Young teach the specific culture conditions to the ordinary artisan that are required by the claims.

Applicants Arguments

Applicants continue that as alleged by the Examiner, Dao suggests the combination of fibronectin and FL to ultimately replace the use of stromal layers in gene transfer protocols (*Office Action dated November 3, 2005,* at p. 3). Applicants continue that the Examiner alleges that an ordinary artisan would have been motivated to use FL in combination with an mpl ligand and fibronectin as taught by Young since Doa teaches that FL might be essential to viability absent stromal support. Accordingly, Applicants argue, an ordinarily skilled artisan would expect fibronectin to replace, or be redundant with, the beneficial effects of stromal support on transduction, particularly in light of the fact that it does not enhance transduction of HSCs cultured with stromal support and in the presence of other cytokines including LF (*Specification,* at Example 9, Figure 9). Applicants continue that an ordinarily skilled artisan would not expect fibronectin to synergize with thrombopoietin (TPO) to enhance gene transfer and in contrast the present application provides evidence that fibronectin unexpectedly synergizes with thrombopoietin to significantly increase transduction of HSCs. These arguments are not persuasive.

Response

Dao teaches and motivates the ordinary artisan to use fibronectin in combination with flt3 ligand when no stromal support is present in the cell culture. While Applicants argue that the

specification teaches that using fibronectin does not enhance transduction of HSC's and that the ordinary artisan would not be motivated to use fibronectin based upon this finding, this argument is not persuasive. Applicants arguments are not drawn to claim limitations, but rather to unexpected properties disclosed in the specification. Again, the claims are merely a method of transducing HSC's under specific culture conditions, which Dao and Young in combination teach.

In summary, the claimed invention broadly encompasses cell culture conditions with which to transduce human pluripotent hematopoietic stem cells with a viral vector. The claims simply recite using specific cellular factors and substrates at a range of concentrations within the culture media. Both Dao and Young provide teaching regarding each of these claim limitations drawn to specific cellular factors and substrates, further though, Dao and Young in combination provide motivation to the ordinary artisan to use an mpl ligand such as TPO in the presence of fibronectin to enhance gene transfer in the $CD34^+$ Thy-l^+ Lin^- cells to be genetically modified.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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